



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

National Health and Nutrition Examination Survey (NHANES)

**Stored Biologic Samples; Proposed Cost Schedule and
Guidelines for Proposals to Use Serum, Plasma, and Urine
Samples**

AGENCY: Centers for Disease Control and Prevention (CDC),
Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: The Centers for Disease Control and Prevention (CDC) in the Department of Health and Human Services (HHS) announces the availability of stored serum, plasma, and urine samples obtained from participants in the National Health and Nutrition Examination Survey (NHANES) and the proposal parameters and fee schedule for use. The National Health and Nutrition Examination Survey (NHANES) is one of a series of health-related surveys conducted by CDC's National Center for Health Statistics (NCHS).

DATES: The stored NHANES biologic samples are available [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The fee structure for these samples is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Bryan Stierman, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Hyattsville, MD 20782.

Telephone: (301) 458-4798. Email: Serumplasmaurine@cdc.gov.

SUPPLEMENTARY INFORMATION:

NHANES is a program of periodic surveys conducted by NCHS. Examination surveys conducted since 1960 by NCHS have provided national estimates of the health and nutritional status of the U.S. civilian non-institutionalized population. The goals of NHANES are: (1) to estimate the number and percent of persons in the U.S. population and designated subgroups with selected diseases and risk factors; (2) to monitor trends in the prevalence, awareness, treatment and control of selected diseases; (3) to monitor trends in risk behaviors and environmental exposures; (4) to analyze risk factors for selected diseases; (5) to study the relationship between diet, nutrition and health; (6) to explore emerging public health issues and new technologies; and (7) to establish and maintain a national probability sample of baseline information on health and nutrition status.

For NHANES cycles prior to the 2021-22 cycle, the survey oversamples the two largest race/ethnicity groups, non-Hispanic black and Mexican American (and all Hispanic since 2007-08). In 2011-2020, NHANES also oversampled the Asian race/ethnicity group.

Sample Availability

Samples are available from NHANES III, a periodic survey

that was conducted from 1988-1994 (see: <https://wwwn.cdc.gov/nchs/nhanes/nhanes3/default.aspx> for more information on NHANES III), and the continuous NHANES, with data release in two-year cycles starting in 1999-2000 through the 2019-March 2020 (Coronavirus Disease 2019 (COVID-19) pre-pandemic) (Table A) collection. NCHS is making both collections available for study proposals.

Approximately 30,000 individuals were examined in NHANES III, which began in the fall of 1988, and ended in the fall of 1994. Investigators can analyze samples from this survey in two phases. Phase 1 was conducted from October 1988 to October 1991 and Phase 2 began October 1991 and ended October 1994.

Beginning in 1999, NHANES became a continuous, annual survey with examination of approximately 5,000 individuals a year and data release every two years. Samples from a single year of the survey will only be provided in emergency situations (outbreaks). Projects must use two-year cycles or multiple two-year cycles for their studies (i.e., 1999-2000, 2001-2002 etc.).

Serum, plasma, and urine samples are stored in two biorepositories. Samples that were initially used for laboratory assays included in the surveys, that were stored at -70°C and that have been through at least two freeze-thaw cycles, are considered surplus samples. They are stored at

a commercial biorepository under contract to NCHS. In addition, another set of serum, plasma, and urine samples were also stored immediately after collection at -80°C or below in vapor-phase liquid nitrogen. These samples have not undergone a freeze-thaw cycle and are considered pristine samples. The CDC Biorepository (CBR) is the long-term repository for the pristine NHANES serum, plasma, and urine samples. NCHS is making both pristine and surplus collections available for study proposals. Please see the NHANES Biospecimen Program series report for details about collection and storage of serum, plasma, and urine samples http://www.cdc.gov/nchs/data/series/sr_02/sr02_170.pdf.

Table A: Overview of biospecimens by survey year, NHANES III (1988-1994) and NHANES 1999-March 2020 (pre-pandemic)						
NHANES Cycle	Sample Type					
	Pristine ¹			Surplus ²		
	Sera	Plasma	Urine	Sera	Plasma	Urine
III (1988-1994)	X			X		
1999-2000	X	X	X	X	X	
2001-2002	X	X	X	X	X	
2003-2004	X	X	X	X		
2005-2006	X	X	X	X		
2007-2008	X	X	X	X	X	
2009-2010	X	X	X	X		
2011-2012	X		X	X		
2013-2014	X		X	X		
2015-2016	X		X	X		
2017-2018	X		X	X		
2019-March pre-pandemic 2020	X		X	X		

¹ Samples immediately frozen for storage, did not undergo laboratory testing.

² Samples are surplus specimens after laboratories had completed testing.

Parameters for sample use:

1. Investigators should justify why they need a national probability sample for their study.
2. To assure the representative nature of NHANES, at least a 1/3 sample of a two-year cycle must be requested for an individual proposal. For details of the sampling design, see the Analytic Guidelines at: <https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx>
3. Investigators that request pristine (never thawed) samples should justify the use of the pristine samples.
4. Only proposals with test results that are determined **not** to have clinical significance for participants will be accepted. Starting in 1999, the consent form informed participants that they would not receive results from any future laboratory analysis that may be conducted on their samples. Though the consent form for NHANES III had less detail, this parameter is also applicable to the use of NHANES III samples.

Therefore, only proposals with laboratory test results that do not have clinical significance to the survey participant will be accepted. The potential for clinical significance of a laboratory test should be addressed by investigators in the proposal; the

determination of clinical significance will be made by the Technical Panel. A laboratory test result is considered clinically significant to the survey participant if the following criteria are met:

- The laboratory test is performed by a Clinical Laboratory Improvement Amendments (CLIA)- certified laboratory deeming the findings valid,
- the findings have significant implications for the participant's health concerns, and
- a course of action is readily available to treat the associated health concern

Proposal Evaluation

All proposals for use of NHANES samples will be evaluated by a Technical Panel, the NCHS Confidentiality Officer, the NCHS Human Subjects Contact and the NCHS Ethics Review Board (ERB). The current Technical Panel consists of NHANES staff: two physicians, one statistician and a laboratory expert. Other experts from inside or outside the Federal Government are added as needed. The Technical Panel reviews proposals for scientific merit to determine: the need to use a nationally representative sample, public health significance, and laboratory assay validity, and potential for clinical significance to the participant. The NCHS Confidentiality Officer reviews for disclosure risk; the NCHS Human Subjects Officer for potential human subjects concerns; and the NCHS ERB for

conforming to the informed consent. The NCHS ERB will review the proposal even if the investigator has received approval by their respective institutional review panel. The proposal, if approved, will become an amendment to the current NHANES ERB Protocol (i.e., the NHANES ERB Protocol that is in effect at the time of the investigator's proposal approval and held at NCHS).

The Technical Panel will evaluate the proposal for the scientific, technical, and clinical significance to the participant, the appropriateness and adequacy of the study design, and the methodology proposed to reach the study goals. See "Procedures for Proposals" below. The proposal should outline how the results from the laboratory analysis will be used. Because NHANES is a complex, multistage probability sample of the U.S. population, the appropriateness of the NHANES sample to address the goals of the proposal will be an important aspect of scientific merit.

Sampling weights are therefore used to make national estimates of frequencies. The use of weights, sampling frame and methods of assessment of variables included in the data are likely to affect the proposed study. For this reason, **investigators submitting proposals are required to request at least a 1/3 sample of a NHANES cycle to maintain the representative nature of the survey.**

The Technical Panel will also review the data analysis

plan and evaluate whether the proposal is an appropriate use of the NHANES samples. The investigators should justify why they need a national probability sample for their study. The Technical Panel review will seek to assure that the proposed project does not go beyond either the general purpose for collecting the samples in the survey, or of the specific stated goals of the NHANES proposal.

Investigators are encouraged to review the NHANES data, survey documents, manuals and questionnaires at: NHANES Questionnaires, Datasets, and Related Documentation (cdc.gov)

or for NHANES III:

<https://wwwn.cdc.gov/nchs/nhanes/nhanes3/datafiles.aspx>

PROCEDURES FOR PROPOSALS:

All investigators (including CDC investigators) must submit a proposal for use of NHANES serum, plasma, or urine samples. Proposals are limited to a maximum of 10 single-spaced typed pages, excluding figures and tables, using at least a size 10 font. The cover of the proposal (which is not included in the 10-page limit) should include the title of the proposal, the name, address, phone number and E-mail address of the principal investigator (PI), and the name of the institution where the laboratory analysis will be done. The name, address, phone number and E-mail address of all additional investigators should also be included on the

cover. All proposals should be E-mailed to Serumplasmaurine@cdc.gov. Proposals from CDC investigators must also include the investigator's Collaborative Institutional Training Initiative (CITI) expiration date.

The following criteria will be used for technical evaluation of proposals:

Proposals should include the following information:

1) Specific Aims: List the broad objectives; describe concisely and realistically what the study is intended to accomplish and state the specific hypotheses to be tested. NHANES is designed to provide prevalence estimates of diseases or conditions that are expected to affect at least 5-10 percent of the population. Proposals that expect much lower prevalence estimates need to provide more detail on why samples from NHANES are needed for the project and provide details on how these data will be analyzed.

2) Background and Public Health Significance: Describe the public health significance, scientific merit, and practical utility of the assay. Briefly describe in 1-2 pages the background of the proposal, identifying gaps in knowledge that the project is intended to fill. State concisely the importance of the study in terms of the broad, long-term objectives and public health relevance including a discussion of how the results will affect public health policy or further scientific knowledge. The

proposal should justify the need for samples that are representative of the U.S. population. The investigator should convey how the results will be used and the relationship of the results to the data already collected in NHANES. The analyses should be consistent with the NHANES mission and the health status variables.

3) Study Design and Methods: Describe the study design, analytic plan, and the procedures to be used. A detailed description of laboratory methods including validity and reliability must be included with references. The volume of sample and number of samples requested must be specified. Adequate methods for handling and storage of samples must also be addressed. The laboratory must demonstrate expertise in the proposed laboratory test including the capability for handling the workload requested in the proposal. The proposal should also include a justification for determination of sample size or a power calculation. If the investigator is requesting a sub-sample of samples, a detailed description and justification must be given.

The Technical Panel will evaluate the Investigator's submitted proposal study design and analysis plan to determine whether the project is consistent with the design of the NHANES survey. The resulting data will be released in the public domain or in rare occasions to the NCHS Research Data Center by NCHS (if there is a disclosure

concern, e.g. one year of NHANES cycle). Released data from sub-samples may be less useful to the scientific community, so such requests will receive a lower priority for obtaining the samples.

4) Clinical Significance of Results: Address the clinical significance to the survey participant of the proposed laboratory test. Since the consent document for sample storage and future studies states that individual results will not be provided to the participant, the investigator must address whether there is evidence that the proposed test results have health implications to the participants and whether knowledge of results would provide grounds for medical intervention (even if many years have passed since the participant was in the survey and the sample collected). Any test with results that are clinically significant, and would require reporting to the participant, is not appropriate for testing on the stored serum, plasma, or urine samples and will not be approved; laboratory testing that is clinically significant should be considered for inclusion in a future NHANES survey cycle see NHANES New Content and Proposal Guidelines ([cdc.gov](https://www.cdc.gov/nhanes/new-content-and-proposal-guidelines)).

5) Qualification: Provide a brief description of the Principal Investigator's expertise in the proposed area, including publications in this area within the last three

years. A representative sample of earlier publications may be listed if this section does not exceed two pages.

6) Period of Performance: Specify the project time period. Substantial progress must be made in the first year that samples have been obtained, and the project should be completed within a reasonable time period. Please discuss the approximate time the investigator expects this project will take to complete the project. The NCHS Project Officer must be consulted about the disposition of the samples. At the end of the project period, any unused samples must be returned to the NHANES Specimen Repository or discarded appropriately.

7) Funding: The source and status of the funding to perform the requested laboratory analysis should be included. Investigators will be responsible for the cost of processing and shipping the samples. The cost per sample is \$15.00. The basis for the cost structure is in the last section of this document. Payment for the samples will be collected before the samples are released.

SUBMISSION OF PROPOSALS:

Proposals can be submitted in MS Word format by E-mail to:
Serumplasmaurine@cdc.gov

Project Timeframes

- Submitting Proposals: Can be submitted on an ongoing basis
- Scientific Review Date (NHANES Technical Panel): Within one month of proposal submission.
- Scientific Review Date (NCHS Human Subjects, Confidentiality and ERB): Within two months of Technical Panel proposal acceptance
- Anticipated distribution of samples: one month after ERB approval and after all Interagency Agreements or Material Transfer Agreements are signed, and fees are paid.

APPROVED PROPOSALS:

Approved projects will be provided samples after receipt of a signed Materials Transfer Agreement (MTA) and a check (written to The Centers for Disease Control and Prevention) for the cost of the samples, or for Federal Government proposals, a signed Interagency Agreement (IAA). All laboratory results obtained from the samples must be sent back to NCHS to be linked to the NHANES variables requested by the investigator and that are needed to perform a quality control review of the data. The results data files will undergo disclosure review by the NCHS Disclosure Review Board or NCHS Confidentiality Officer or designee before the linked data are sent to the

investigator for quality control review. Once approved by disclosure review and after the investigator has signed the Data Sharing Agreement or a Designated Agent Agreement (respectively "Agreement"), the linked data file will be sent to the investigator for use pursuant to the terms of the relevant agreement. The quality control review must take place within 60 days and the return of the data to NCHS within the next 30 days so these data may be released to the public.

AGENCY AGREEMENT:

A formal signed agreement in the form of an MTA or an IAA with investigators who have projects approved will be completed before the release of the samples to the investigator. This agreement will contain the conditions for use of the samples as stated in this Federal Register Notice and as agreed upon by the investigators and CDC.

CONTINUATIONS:

A brief progress report will be submitted annually to NHANES. This report should describe work completed and timeline to project completion. If five years have elapsed since the initial approval of the protocol by the NCHS ERB a more detailed plan and timeline to complete the study will be required by NHANES. If at any time during the project a new investigator(s) are added or the Principal

Investigator has changed, the NHANES Serum/plasma/urine Project Officer must be notified.

DISPOSITION OF RESULTS AND SAMPLES:

No samples provided can be used for any purpose other than those specifically requested in the proposal and approved by the NHANES Technical Panel and the NCHS ERB. No samples can be shared with others, including other investigators, unless specified in the proposal and so approved by the NHANES Technical Panel and the NCHS ERB. Any unused samples must be returned to the NHANES Serum, Plasma and Urine Repository or disposed of, after NHANES approval, upon completion of the approved project. The results, once returned to NCHS, will be part of the public domain. The investigator will have 60 days for quality control review of the data before public release by NHANES.

COST SCHEDULE FOR PROVIDING NHANES SAMPLES:

There is a nominal processing fee of \$15.00 for each sample received from an NHANES Serum, Plasma and Urine Repository. If the investigator requests to use the samples for another project after the completion of the initial project, the additional cost will be \$5.50 per sample to handle the processing of the data and management of the subsequent proposal process. A new proposal must be submitted and go through the approval process before any

additional use of the samples. The costs include the collection, processing, storage, and retrieval of the samples along with the review of proposals and the preparation of the data files. The costs listed are for the recurring laboratory materials to dispense and prepare the samples during collection and for shipping. The costs for the NHANES repository include long term storage (including inventory management and materials and equipment) and accessioning of samples and pulling samples from the freezer for shipment to the investigator. Labor costs are based on a proposal administrator to manage the proposal process and computer programmers at NCHS who prepare the data files for the release of the data along with documentation on the NHANES Web page.

Elements of the Fee for NHANES Biologic Samples

Cost Factors	Cost Per Vial
Material and Equipment	\$3.42
Processing the samples (Receiving, handling, and shipping)	\$2.58
Inventory management	\$1.80
Administrative, management of the proposal process.	\$1.65
Preparation of data files	\$3.85
SUBTOTAL	\$13.30
CDC Support (5%)	\$0.67

SUBTOTAL	\$13.97
NCHS Support (7.50%)	\$1.05
TOTAL	\$15.00*

- Total is rounded down from \$15.02

Authority: Sections 301,306 and 308 of the Public Health Service Act (42 U.S.C. 241,242k and 242m).

Dated: August 9, 2021.

Sandra Cashman,

Executive Secretary,

Centers for Disease Control and Prevention.

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